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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/809,662	03/15/2001	Steven Stice	235.0032 0101	5744

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EXAMINER	
CROUCH, DEBORAH	

ART UNIT	PAPER NUMBER
1632	16

DATE MAILED: 07/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/809,662	STICE, STEVEN	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this c mmunication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *198-225 and 229-263* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *198-225 and 229-263* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Applicant's arguments filed May 9, 2003 in paper no. 15 have been fully considered but they are not persuasive. The amendment has been entered. Pending claims are 197-225 and 229-263.

The rejection of claims 197 and 220-225 under 35 U.S.C. 112, second paragraph, in office action mailed November 6, 2002 in paper no. 10 has been overcome by applicant's amendments to the claims.

The rejection of claims 197, 199, 200, 206, 208, 209, 212, 214, 220, 222 and 227 rejected under 35 U.S.C. 102(b) in the office action mailed November 6, 2002 in paper no. 10 has been overcome by applicant's amendments to the claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 221-225, 231 and 233-263 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing a cloned non-human mammalian NT embryo, the method comprising introducing a donor nucleus into an oocyte enucleated either before or after transfer of the donor nucleus to yield a cloned nonhuman mammalian NT embryo and activating the embryo, wherein the donor nucleus introduced into the oocyte is obtained from a donor cell that is arrested at late G1 phase and methods of producing a cloned nonhuman mammal comprising transferring the embryo to a host female of the same species, does not reasonably provide enablement for a method of producing a cloned non-human mammalian NT embryo, the method comprising introducing a donor genetic material into an oocyte to yield a cloned nonhuman mammalian NT embryo, wherein the donor genetic material introduced into the oocyte is obtained from a donor cell that is arrested at late G1 phase for reasons presented

in the office action mailed November 6, 2002 in paper no. 10. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Further, the enablement rejection that the only type of donor genetic material enabled is a donor nucleus is maintained. Applicant argues that at the time of filing that it was known to the skilled artisan that chromosomes could be transferred to recipient cells without damage to the chromosome. Applicant has supplied Compton et al. in support of this allegation.

Compton is drawn to method of isolating YAC's from yeast cells without damage to the artificial chromosome. However, Compton states that their method is applicable to YAC's up to 1 Mb (page 1762, col. 2, parag. 1, lines 1-3). The chromosomes in mammals are considerably larger. Further, Compton doesn't provide a method through which to isolate one YAC. In the mixture prepared my Compton are multiple copies of the same YAC, and therefore multiple copies of the same chromosome. In nuclear transfer there must be on two copies of each chromosome. Multiple copies of chromosomes set up an abnormal situation so that development of the embryo is prevented. Additionally, for mitosis, the chromosomes need to be associated with a nuclear skeleton. Chromosomes randomly inserted into an enucleated oocyte, or an oocyte that is enucleated subsequent to transfer of the donor nucleus will not be associated with a nuclear skeleton. Thus, the only genetic material enabled for NT is a nucleus, be it isolated or within a cell.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 197-202, 204, 206, 208, 209, 211, 212, 214, 218-225, 229-235, 237, 239, 241, 242, 244, 245, 247, 251-259 and 261-263 remain rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,945,577 issued August 31, 1999 (Stice) in view of Collas et al (1992) Biol. Reprod. 46, 492-500 and Alessi et al (1988) Expt. Cell Res. 245, 8-18 for reasons presented in the office action mailed November 6, 2002 in paper no. 10.

Stice teaches methods of cloning by nuclear transfer where the donor cell can be fibroblast, an epithelial cells, a hematopoietic cells or a lymphocyte, which also represent adult or cultured cells, or that the donor cell can be from ectoderm, mesoderm or endoderm, which are late stage embryo cells (col. 8, lines 4-15). Stice specifically describes the culture of fetal fibroblast cells, which are then used as nuclear donors (col. 15, liens 51 to col. 16, line 11 and col. 16, lines 57-60). Stice states that the method cloning via nuclear transfer can be used to clone pigs and bovines (claim 13). Stice teaches that the insertion of an isolated nucleus in some instances is preferable (col. 10, lines 10-15). Collas teaches the production of rabbit NT embryos by transferring a donor blastomere cell that had been synchronized at the G1/S boundary into an enucleated oocyte (page 494, col. 1-2, bridg. Parag.). Collas teaches the disaggregation of rabbit embryos into their blastomere components and incubating the blastomeres, first in colcemid followed by release and synchronization at the G1/S boundary by incubation in aphidicolin (page 494, col. 1, parag. 3, line 7 to col. 2, line 2; and col. 2, parag. 1, lines 1-8). Collas refers to this procedure as "arrest" of embryos in G1 (page 494, col. 2, parag. 2, lines 6-10). Collas offers motivation in stating that an enhanced rate of development was seen in nuclear transfer embryos to blastocysts with donor nuclei in the G1 phase, 71% (abstract). Alessi teaches that olomucine and roscovitine are CDK2 Kinase inhibitors and arrest human fibroblasts in G1 (page 14, col. 2, parag. 1, lines 1-5). Thus, it would have been obvious to the ordinary artisan to modify the method of producing NT embryos as taught by Stice where the donor

cell was from a proliferating cell culture with the method of producing cloned NT embryos where the donor cells were arrested in G1 prior to transfer as taught by Collas to obtain a greater number to blastocysts, and where the arrest was by incubation in the presence of olomucine or roscovitine. Stice offers motivation by teaching that blastocyst production by the method disclosed therein was 10% (col. 17, lines 40-41).

Claims 197, 202, 203, 231 and 236 remain rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,945,577 issued August 31, 1999 (Stice) in view of Collas et al (1992) Biol. Reprod. 46, 492-500 and Wakayama et al (1998) Nature 394, pages 369-374 for reasons presented in the office action mailed November 6, 2002 in paper no. 10.

Stice teaches methods of cloning by nuclear transfer where the donor cell can be fibroblast, an epithelial cells, a hematopoietic cells or a lymphocyte, which also represent adult or cultured cells, or that the donor cell can be from ectoderm, mesoderm or endoderm, which are late stage embryo cells (col. 8, lines 4-15). Stice specifically describes the culture of fetal fibroblast cells, which are then used as nuclear donors (col. 15, liens 51 to col. 16, line 11 and col. 16, lines 57-60). Stice states that the method cloning via nuclear transfer can be used to clone pigs and bovines (claim 13). Stice teaches that the insertion of a isolated nucleus in some instances is preferable (col. 10, lines 10-15). Collas teaches the production of rabbit NT embryos by transferring a donor blastomere cell that had been synchronized at the G1/S boundary into an enucleated oocyte (page 494, col. 1-2, bridg. Parag.). Collas teaches the disaggregation of rabbit embryos into their blastomere components and incubating the blastomeres, first in colcemid followed by release and synchronization at the G1/S boundary by incubation in aphidicolin (page 494, col. 1, parag. 3, line 7 to col. 2, line 2; and col. 2, parag. 1, lines 1-8). Collas refers to this procedure as "arrest" of embryos in G1 (page 494, col. 2, parag. 2, lines 6-10). Collas offers motivation in stating that an enhanced rate of development was seen in nuclear transfer embryos to

blastocysts with donor nuclei in the G1 phase, 71% (abstract). Wakayama teaches the production of cloned mice using cumulus cells as nuclear donors (page 370, Table 1). Stice offers motivation by teaching that blastocyst production by the method disclosed therein was 10% (col. 17, lines 40-41). Collas offers motivation in stating that an enhanced rate of development was seen in nuclear transfer embryos to blastocysts with donor nuclei in the G1 phase, 71% (abstract). Wakayama offers motivation in that a blastocyst development rate of 39% was reported (page 370, Table 1). Thus, it would have been obvious to the ordinary artisan to modify the method of producing NT embryos as taught by Stice where the donor cell was from a proliferating cell culture with the method of producing cloned NT embryos where the donor cells were arrested in G1 prior to transfer as taught by Collas, where the donor cells were cumulus cells, a taught by Wakayama in order to obtain a greater number to blastocysts.

Claims 197, 205, 231 and 238 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Collas et al (1992) Biol. Reprod. 46, pages 492-500 in view of Cibelli et al (1998) Science 280, pages 1256-1259 for reasons presented in the office action mailed November 6, 2002 in paper no. 10.

Collas teaches the production of rabbit NT embryos where the donor cell was synchronized at the G1/S boundary (page 494, col. 1-2, bridg. Parag.). Collas teaches the disaggregation of rabbit embryos into their blastomere components and incubating the blastomeres, first in colcemid followed by release and synchronization at the G1/S boundary by incubation in aphidicolin (page 494, col. 1, parag. 3, line 7 to col. 2, line 2; and col. 2, parag. 1, lines 1-8). Collas refers to this procedure as "arrest" of embryos in G1 (page 494, col. 2, parag. 2, lines 6-10). Collas does not teach the production of NT embryos where the donor nucleus contains transgenic DNA. However, Cibelli teaches the production of NT embryos where the donor nucleus contains a β-galactosidase-neomycin resistance fusion

gene driven by a CMV promoter (page 1256, col. 3, parag. 1, lines 1-16 and page 1257, col. 1, parag. 1, lines 1-3). Cibelli offers motivation in stating that the donor cells were not synchronized in G1, but that FACS analysis showed that 56% of the cells were in G1 and that this would provide a large population that could support development (page 1257, col. 3, parag. 1). Cibelli also states that the donor cells should be in G1 (page 1256, col. 3, lines 7-10). Collas offers motivation in stating that a high rate of development to the blastocyst stage was obtained using G1 synchronized donors (page 499, col. 1parag. 3, lines 4-7).

Claims 197, 206, 212, 213, 231 and 246 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Collas et al (1992) Biol. Reprod. 46, 492-500 in view of Yang et al, (1992) Biol. Reprod. 46, supply. No. 1, page 117, Abs. 268 for reasons presented in the office action mailed November 6, 2002 in paper no. 10.

Collas teaches the production of rabbit NT embryos where the donor cell was synchronized at the G1/S boundary (page 494, col. 1-2, bridg. Parag.). Collas teaches the disaggregation of rabbit embryos into their blastomere components and incubating the blastomeres, first in colcemid followed by release and synchronization at the G1/S boundary by incubation in aphidicolin (page 494, col. 1, parag. 3, line 7 to col. 2, line 2; and col. 2, parag. 1, lines 1-8). Collas refers to this procedure as "arrest" of embryos in G1 (page 494, col. 2, parag. 2, lines 6-10). Yang teaches methods of activating matured oocyte in the presence of cyclohexamide (lines 4-6). Yang teaches that cyclohexamide and electrofusion combined resulted in the activation of 90% of the oocytes (lines 20-27). Collas offers motivation in stating that an enhanced rate of development was seen in nuclear transfer embryos to blastocysts with donor nuclei in the G1 phase, 71% (abstract). Thus, it would have been obvious to the ordinary artisan to modify the method of producing NT embryos as taught by Collas with the method of activation described by Yang to prevent the meiotic arrest of mater oocytes so that a greater number of functional NT units could be produced.

Claims 197, 206, 207, 231, 239 and 240 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Collas et al (1992) Biol. Reprod. 46, 492-500 in view of Campbell et al (1996) Nature 380, 64-66 for reasons presented in the office action mailed November 6, 2002 in paper no. 10.

Collas teaches the production of rabbit NT embryos where the donor cell was synchronized at the G1/S boundary (page 494, col. 1-2, bridg. Parag.). Collas teaches the disaggregation of rabbit embryos into their blastomere components and incubating the blastomeres, first in colcemid followed by release and synchronization at the G1/S boundary by incubation in aphidicolin (page 494, col. 1, parag. 3, line 7 to col. 2, line 2; and col. 2, parag. 1, lines 1-8). Collas refers to this procedure as "arrest" of embryos in G1 (page 494, col. 2, parag. 2, lines 6-10). Campbell teaches the "preactivation" of oocytes, prior to introduction of a donor nucleus (page 64, col.2 , parag. 1, lines 13-16). Campbell offers motivation in stating that the prior activation of a recipient oocyte overcomes donor cell cycle stage effects by reducing MPF activity and subsequent donor chromosome damage (page 64, col. 1, parag. 3, lines 1-9). Thus at the time of the instant invention, it would have been obvious to the ordinary artisan to modify the method of Collas by preactivating the recipient oocyte so that MPF activity would be lower and lessen the chance of damage to the donor chromosomes as taught by Campbell.

Claims 210, 215-217, 243, 248-250 and 260 appear to be free of the prior art.

The obviousness rejections have been restated to concur with applicant's claim amendments and new claims. Further, as applicant argued the art rejections together, these arguments will be answered together.

Applicant argues that the office action fails to set forth a suggestion in the art to substituted a CDK2 inhibitor for aphidicolin in a nuclear transfer procedure. Applicant argues that Alessi investigated CDK2 inhibitors for purely experimental reasons to identify

substrates for these kinases and that these inhibitors are tool to inhibit tumor cell growth. Applicant argues that this does not provide motivation to substitute CDK2 inhibitors for the polymerase inhibitor, aphidicolin. Applicant argues that the skilled artisan would not be motivated to use a chemical that kills cells or inhibits tumor cell growth in process designed to promote life. These arguments are not persuasive.

The skilled artisan with the teachings of the cited prior art would know from Stice and Collas that nuclear transfer can be successfully achieved using a somatic nucleus as the donor, and where the donor cells are arrested in G1 by aphidicolin. It is Alessi's teachings that nuclei could be arrested in G1 using CDK2 inhibitors, olomucine and roscovitine, that would provide the motivation. The exact method used by Alessi, that is the inhibition of growth of tumor cells, would not be seen as relevant to by skilled artisan who would know that the inhibition of growth of any nucleus will result in death of the nucleus if the inhibition is allowed to continue. Even in donor cells for nuclear transfer if left for a sufficient period of time in the presence of aphidicolin. All the skilled artisan would be doing is substituting one G1 arresting agent for another, and combination of art provides this teaching.

Applicant argues that there is no expectation of success that a CDK2 inhibitor could be substituted for a DNA polymerase inhibitor in a nuclear transfer method. Applicant argues that without knowledge of what harmful side-effects a CDK2 inhibitor would have on other biological pathways in the cell cycle, the effect of the inhibitor on activation, or the effect of the inhibitor on development, the scientist would have no expectation that a CDK2 inhibitor would actually work. These arguments are not persuasive.

The requirement is "a reasonable expectation of success" and not an absolute expectation of success. Experimentation is permitted within 103, and thus the skilled artisan is permitted to perform experimentations. In fact, the art teaches that CDK2 inhibitors do arrest in G1, as does aphidicolin.

Applicant argues that Alessi teaches away from the use of a CDK2 inhibitor instating that the identity of the protein substrates of these kinases is far from being completely discovered. This argument is not persuasive.

First, a teaching away is a statement that a particular method would not work, and thus the artisan would be dissuaded from using that method. Alessi does not teach such. Further, it is not clear exactly why applicant believes the lack of knowledge of CDK2 inhibitor substrates would prevent the ordinary, the appropriate level of skill for obviousness, from using these chemicals to arrest donor cells in G1. Until any methodology is actually performed the absolute outcome is not known. However, as stated above, absolute success is not the requirement for 103.

Applicant argues that the skilled artisan would not be motivated to inhibit using CDK2 inhibitors because, unlike aphidicolin, it was not known that the arrest of cells in G1 by CDK2 inhibitors would increase nuclear transfer efficiencies. Applicant explains that CDK2 inhibitors and aphidicolin act by different mechanisms. This argument is not persuasive.

Applicant appears to be arguing that the lack of an anticipatory rejection prevents the making of an obviousness rejection. Again, this incorrect. While it is true that no reference inhibits nuclear transfer donor cells with CDK2 inhibitors, the art teaches that such inhibitors arrest cells in G1. There is no requirement that the mechanism of the art be know for the art to applied, and there is no requirement for guaranteed success. As stated before experimentation is permitted. There is a reasonable expectation of success as the art clearly taught the inhibition of cells in G1 using CDK2 inhibitors. Further, applicant is reminded that claims 231-258 merely claim arrest in G1 and claim 259 states aphidicolin. For these claims, applicant is arguing CDK2 inhibitors but the claims are not so limited.

Applicant argues that, with regard to the teachings of Collas regarding the use of aphidicolin to arrest donor blastomers in G1 would not motivate the skilled artisan to arrest

donor somatic cells in G1. Applicant argues that the cell cycle for blastomers is very different from that of somatic cells. Applicant argues that blastomeres have a short G1 as opposed to somatic cells. Applicant argues that because of these differences in G1 the skilled artisan would have no expectation that arresting somatic cells in G1 would improve developmental rates similarly to those shown by Collas. These arguments are not persuasive.

The benefit demonstrated by Collas was that donor blastomeres that were arrested in G1 provided better rates of blastocyst development. It is not seen how the length of the G1 phase in blastomeres versus somatic cells would affect the outcome of Collas. The benefit was the arresting cells in G1. Somatic cells would also be so inhibited. Collas says nothing about the inherent length of G1 in blastomeres being relevant to the outcome of the incubation of blastomeres in aphidicolin. Rather from reading Collas, the arrest in G1 prevents damage to chromosomes (see page 499). Thus, the increased blastocyst production seen in Collas through the arrest of donor blastomeres in G1 is not related to the inherent length of G1 in the donor cells but in the prevention of chromosome damage if the donor cells are not so arrested. This effect would reasonable be expected in somatic cells.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant

to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 703-308-1126. The examiner can normally be reached on M-Th, 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Deborah Crouch

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

dc
July 28, 2003